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ORIGINAL ARTICLE

Prescriptions for angiotensin-converting enzyme inhibitors/angiotensin receptor blockers and monitoring of serum creatinine and potassium in patients with chronic kidney disease

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Abstract Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEIs/ARBs) are commonly used in patients with chronic kidney disease (CKD). We studied the status of ACEI/ARB prescriptions and serum creatinine (Scr) and potassium monitoring in CKD patients. A retrospective observational study was conducted on patients who had at least two sets of Scr data at outpatient visit. Estimated glomerular filtration rate (eGFR) based on the second Scr value was calculated using the Modification of Diet in Renal Disease four-variable equation. CKD was defined and staged according to the National Kidney Foundation Disease Outcomes Quality Initiative Guideline. Patients with diabetes and/or hypertension with an eGFR over 60 mL/min/1.73 m^2 and without proteinuria were defined as the CKD-at-risk group. The percentages and factors associated with ACEI/ARB prescription and Scr and potassium monitoring were calculated and analyzed by logistic regression. Among the 5714 subjects included, ACEIs/ARBs were prescribed to over 50% of patients in the CKD-at-risk group and in CKD stages 1–5. After adjusting for age, sex, potassium level, eGFR, and co-morbidities, the odds ratios for prescriptions of ACEIs/ARBs were 1.66 [95% confidence interval (CI) 1.44–1.91, $p < 0.001$) and 2.80 (95% CI 2.12–3.70, $p < 0.001$) in CKD stage 3, and

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stages 4 and 5, respectively, compared with the reference group (eGFR≥60 mL/min/1.73 m^2). During the year of ACEI/ARB treatment, Scr was monitored in 91.6% of ACEI/ARB-treated patients, while potassium was monitored in only 38.1%. Renal function status was the independent factor for monitoring of Scr and potassium. In conclusion, prescription of ACEIs/ARBs was common in all stages of CKD. Most patients underwent Scr monitoring, but potassium monitoring was less frequent, and this should be improved in clinical practice.

Introduction

Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) have been suggested by various clinical guidelines for the treatment of patients with chronic kidney disease (CKD) to delay deterioration in renal function [1—3], especially as the preferred agents for diabetic and non-diabetic kidney diseases with proteinuria [4—7]. However, the use of ACEIs/ARBs is associated with untoward effects such as hyperkalemia [8], acute renal failure [9], and cough [8]. It is recommended that blood levels of potassium and creatinine are monitored at the beginning of prescription and thereafter to prevent adverse side effects in patients receiving ACEI/ARB treatment [10].

However, information related to ACEI/ARB prescription in CKD patients and status of serum creatinine (Scr) and potassium monitoring after prescription is lacking in Taiwan. This study aimed to explore the status of prescription of ACEIs/ARBs, the monitoring of Scr and potassium, and the factors associated with monitoring after ACEI/ARB prescription in CKD patients.

Patients and methods

Study subjects

This retrospective study was conducted at a regional teaching hospital in southern Taiwan. Through the hospital informatics system, 21,708 subjects who had Scr measurements during an outpatient visit from January 1, 2004 to December 31, 2005 were screened. The demographics, disease codes [International Classification of Diseases, Clinical Modification, 9th Revision (ICD-9-CM)], pharmacy dispensations, and laboratory data on the patients records were collected from January 1, 2003 to December 31, 2006. After excluding subjects with only a single Scr measurement, those with acute conditions (13,583), those younger than 18 years (535), patients receiving dialysis (277), those with an eGFR >60 mL/min/1.73 m^2 but no diabetes, hypertension, or proteinuria (1592), and patients with incomplete ethnic data (7), a total of 5714 patients were finally included in this study.

Definitions of groups and co-morbidities

Estimated glomerular filtration rate (eGFR), calculated from second Scr measurement by the Modification of Diet in Renal Disease four-variable equation [11,12], was defined as subject's baseline renal function. Proteinuria/albuminuria was defined as at least two occasions of urine protein 1+ or greater on urinalysis by dipstick test, a quantitative measurement of the urine protein to creatinine ratio exceeding 150 mg/g, or a urine albumin to creatinine ratio exceeding 30 mg/g during the year before baseline.

Based on the above data, CKD was identified and staged according to National Kidney Foundation Disease Outcomes Quality Initiative (NKF-K/DOQI) definitions [13], and patients in stage 3 CKD were further divided into groups with stage 3a (eGFR of 45—59 mL/min/1.73 m^2) and stage 3b (eGFR of 30—44 mL/min/1.73 m^2) disease. Patients of diabetes and/or hypertension who had an eGFR of over 60 mL/min/1.73 m^2 but no proteinuria were categorized as the CKD-at-risk group.

Patients who had at least one prescription for ACEIs/ARBs (excluding those irregular regimens, such as Stat or 'as required') 1 year after baseline were categorized as the ACEI/ARB group ($n = 3202$), in contrast to the non-ACEI/ARB group ($n = 2512$). To study the status of laboratory monitoring in patients receiving long-term ACEIs/ARBs, Scr and potassium were traced from the first ACEI/ARB dispensing date for 995 patients who had received ACEI/ARB treatment for 1 year with a dispensing gap of less than 60 days within that year.

Based on ICD-9 codes, diabetes (ICD-9-CM 250.x, 357.2, 362.0x, and 366.41) and hypertension (ICD-9-CM 362.11, 401.x-405.x, and 437.2) were defined as at least two outpatient diagnoses or one inpatient diagnosis before the baseline date.

Statistical analyses

Results were summarized as mean ± standard deviation for continuous variables and proportions for nominal variables. Logistic regression was calculated for crude and independent associations between potential influenced factors (demographic factors, co-morbidities, and laboratory data), the prescription of ACEIs/ARBs, and monitoring of Scr and potassium after treatment. Multivariable analysis was expressed by odds ratios (ORs) and the corresponding 95% confidence intervals (CIs). All analyses were performed using SPSS 12.0 (SPSS Inc., Chicago, IL, USA) for Windows, with $p < 0.05$ considered statistically significant. This study was approved (IRB: KMHK-IRB-96002) by the Institutional Review Board of Municipal Kaohsiung Hsiao-Kang Hospital.

Results

Characteristics of study populations

The demographic, laboratory, and co-morbidity characteristics of the 5714 study patients are listed in Table 1. Their

Table 1 Demographic and clinical characteristics of study subjects grouped by categories of chronic kidney disease (CKD).

Characteristics	Overall	CKD category					
		CKD-at-risk	Stages 1 and 2	Stage 3a	Stage 3b	Stage 4	Stage 5
Number of patients	5714	2094	307	2065	802	261	185
Demography							
Age (y)	61.4 ± 12.6	56.1 ± 11.5	53.5 ± 13.4	64.2 ± 11.2	68.3 ± 11.4	68.6 ± 11.9	64.1 ± 11.9
Male [*n*, (%)]	3103 (54.3)	1201 (57.4)	175 (57.0)	1081 (52.3)	424 (52.9)	135 (51.7)	87 (47.0)
Co-morbidities [n, (%)]							
DM alone	1466 (25.7)	785 (37.5)	105 (34.2)	347 (16.8)	150 (18.7)	49 (18.8)	30 (16.2)
HTN alone	1762 (30.8)	757 (36.2)	44 (14.3)	614 (29.7)	216 (26.9)	74 (28.4)	57 (30.8)
DM and HTN	1487 (26.0)	552 (26.4)	102 (33.2)	461 (22.3)	240 (29.9)	80 (30.7)	52 (28.1)
Neither DM nor HTN	999 (17.5)	0 (0.0)	56 (18.2)	643 (31.1)	196 (24.4)	58 (22.2)	46 (24.9)
Laboratory data (baseline)							
Serum creatinine (mg/dL)	1.46 ± 1.07	1.04 ± 0.16	1.05 ± 0.15	1.28 ± 0.19	1.68 ± 0.28	2.65 ± 0.55	6.22 ± 2.47
eGFR (mL/min/1.73 m^2)	55.7 ± 17.0	70.49 ± 8.0	70.9 ± 8.4	53.2 ± 4.2	38.8 ± 4.2	23.2 ± 4.2	9.6 ± 3.2
Potassium (mmol/L) (number with potassium data)	4.21 ± 0.54 (n = 2037)	4.06 ± 0.42 (n = 441)	4.09 ± 0.53 (n = 111)	4.12 ± 0.47 (n = 676)	4.25 ± 0.52 (n = 435)	4.43 ± 0.60 (n = 204)	4.69 ± 0.72 (n = 170)

Data are expressed as mean ± standard deviation or number and percentage.
DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; HTN = hypertension.

average age was 61.4 ± 12.6 years, 54.3% were male, and 56.8% had hypertension. The average Scr and eGFR at baseline were 1.46 mg/dL and 55.7 mL/min/1.73 m^2, respectively, in all study patients.

Prescription of ACEIs/ARBs

ACEIs/ARBs were prescribed to 3202 patients (56.0%) within 1 year from baseline. Patients in the ACEI/ARB group were older (62.4 ± 12.5 vs. 60.3 ± 12.9 years, $p < 0.001$) and had worse renal function (eGFR 53.6 ± 17.5 vs. 58.4 ± 15.9 mL/min/1.73 m^2, $p < 0.001$) than the non-ACEI/ARB group, and a significant proportion of patients had diabetes and/or hypertension.

Fig. 1 shows the percentages of ACEI/ARB prescriptions according to co-morbidity and stratified by level of eGFR or Scr. The percentages of ACEI/ARB prescriptions were 50.2% of CKD-at-risk, 67.1%, 51.2%, 69.7%, 80.1%, and 64.3% in CKD stage 1 and 2, 3a, 3b, 4 and 5, respectively (Fig. 1, upper panel). The percentage declined in patients with stage 5 CKD.

In patients with an Scr below 1.5 mg/dL, 52.5% received ACEI/ARB medications. This increased to 82.0% of patients with an Scr between 3.0 and 4.4 mg/dL, but decreased to 58.2% of patients with an Scr exceeding 6.0 mg/dL. A higher percentage of patients with an Scr below 4.5 mg/dL received prescriptions, but once the Scr increased to over 4.5 mg/dL, the percentage decreased (Fig. 1, lower panel).The prescription percentages were highest in the group of patients with both diabetes and hypertension compared with those of other groups (Fig. 1).

Factors associated with prescription of ACEIs/ARBs

Lower renal function, diabetes, and hypertension were associated with higher ACEI/ARB prescription percentages, as shown in Table 2. Compared with the group with an eGFR of above 60 mL/min/1.73 m^2, the group with an eGFR between 30 and 59 mL/min/1.73 m^2 (OR 1.66, 95% CI 1.44–1.91, $p < 0.001$) had a higher probability of ACEI/ARB prescription, as did the group with an eGFR below 30 mL/min/1.73 m^2 (OR 2.80, 95% CI 2.12–3.70, $p < 0.001$), compared with the reference group, who had an eGFR≥ 60 mL/min/1.73 m^2. The presence of diabetes or hypertension was also associated with a higher probability of ACEI/ARB prescription than the absence of either diabetes or hypertension, and the prescription percentage was even higher in patients who had both diabetes and hypertension (Table 2).

Monitoring of serum creatinine and potassium

Overall, 911 patients (91.6%) had at least one follow-up Scr measurement (not including the first two Scr readings) within the study period, including 89.6% of the CKD-at-risk group, 87.9% of those with stages 1 and 2 CKD, 89.6% with stage 3a, 93.8% with stage 3b, 97.5% with stage 4, and 100.0% with patients with stage 5 disease, as shown in the upper panel of Fig. 2. The percentage who underwent potassium monitoring was much lower than that for Scr, and only 379 patients (38.1%) had potassium measurements. The percentages

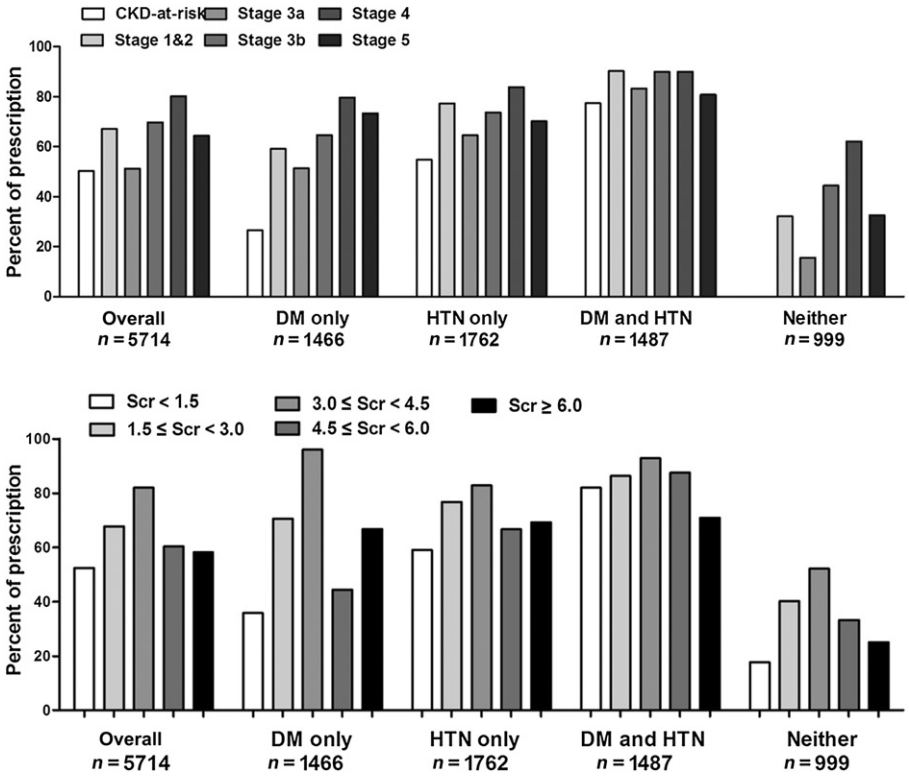

Figure 1. Percentages of angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACEI/ARB) prescriptions in all patients and patients with diabetes (DM) only, hypertension (HTN) only, both DM and HTN, or neither, stratified by stage of chronic kidney disease (CKD; upper panel) and by serum creatinine (Scr) level (lower panel).

increased with the severity of CKD—30.3% in patients with CKD stages 1 and 2, but 72.8% and 94.8% in patients with CKD stage 4 and stage 5, respectively (Fig. 2, upper panel). A similar pattern could be noted in groups classified by the levels of Scr and potassium, as shown in Fig. 2.

Factors associated with laboratory monitoring

Multiple logistic regression analysis of all variables showed that low renal function and the presence of diabetes were associated with an increased likelihood of Scr monitoring, as shown in Table 3. Patients with lower renal function and with previous potassium measurement showed an increased likelihood of potassium monitoring. Patients with baseline potassium data were more likely than those without to be monitored for potassium level (OR 4.98, 95% CI 3.66—6.79, $p < 0.001$) (Table 3).

Discussion

Use of ACEIs/ARBs in CKD patients is recommended by various clinical practice guidelines in order to delay deterioration in renal function [1—3]. We demonstrated that regardless of whether the patients were in the CKD-at-risk group or had different stages of CKD, over half of them were prescribed ACEIs/ARBs. The percentage even reached 80% in CKD with co-morbidities of both diabetes and hypertension. These findings reveal the positive attitude of physicians in terms of following the suggestions in the guidelines and using ACEIs/ARBs in a significant portion of CKD patients.

However, the prescription percentages for ACEIs/ARBs in CKD patients in this study were even higher than those seen in other studies, with percentages of around 50—74% [14—18]. The reasons for this are diverse, but differences in age, the era in which the study was carried out, and awareness of the effect of ACEIs/ARBs among physicians could be explanations. The most dominant population in previous studies [15] was those above 65 years of age, in contrast to our study, which had an average age of 64.5 years. Senior age (> 65 years) is one of factors that might lead to an acute rise in Scr level [19], and an under use of ACEIs/ARBs could reflect fear of an increased risk for acute renal failure or hyperkalemia in elderly patients. The difference in study period between Nissenson's study (1994—1997) [15] and our own (2004—2006) may indicate that physicians today are more familiar with the usage of ACEIs/ARBs, and hence use them more frequently.

Since the adverse effects of the ACEIs/ARBs might be occurring in patients with advanced CKD, this might decrease the willingness and frequency of use. Berger et al. [20] reported that approximately half of patients with chronic heart failure with a GFR below 30 mL/min received ACEIs/ARBs, and Hsu et al. [21] found that only 27% of patients with hypertension and a creatinine clearance of 21—40 mL/min were given ACEIs/ARBs. However, in our results, despite the prescription percentage of ACEIs/ARBs declining in stage 5 CKD patients, the overall percentages of ACEI/ARB prescription were still very high in patients with stages 4 and 5 CKD compared with those seen in other studies [20,21].

Table 2 Factors associated with use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers among the study population ($n = 5714$).

Characteristics	Unadjusted			Adjusted		
	Odds ratio	95% CI	*p*	Odds ratio	95% CI	*p*
Age ($\leq$50 y as reference)						
51–64	1.55	1.34–1.79	<0.001	1.00	0.85–1.18	0.98
65	1.25	1.09–1.45	<0.001	1.01	0.85–1.20	0.95
Sex (female as reference)	1.07	0.96–1.19	0.20	1.22	1.09–1.38	<0.001
eGFR (mL/min/1.73 m^2, $\geq$60 as reference)						
30–59	1.18	1.06–1.31	<0.001	1.66	1.44–1.91	<0.001
<30	2.53	2.02–3.17	<0.001	2.80	2.12–3.70	<0.001
Potassium (mmol/L, without K^+ data at baseline as reference)						
<3.5	1.56	1.08–2.23	0.02	1.24	0.83–1.86	0.29
3.5–5.5	2.13	1.89–2.39	<0.001	1.87	1.63–2.14	<0.001
>5.5	2.53	1.21–5.27	0.01	1.91	0.81–4.55	0.14
Co-morbidities (neither as reference)						
DM alone	2.05	1.72–2.45	<0.001	2.98	2.46–3.61	<0.001
HTN alone	4.89	4.12–5.81	<0.001	6.57	5.45–7.91	<0.001
DM and HTN	14.09	11.58–17.14	<0.001	19.42	15.71–24.01	<0.001

Statistical analysis was carried out using a multiple logistic regression model with adjustment for age, sex, eGFR, potassium level, and co-morbidities, and expressed as odd ratios with 95% confidence intervals. A value $p < 0.05$ was considered statistically significant.
DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; HTN = hypertension.

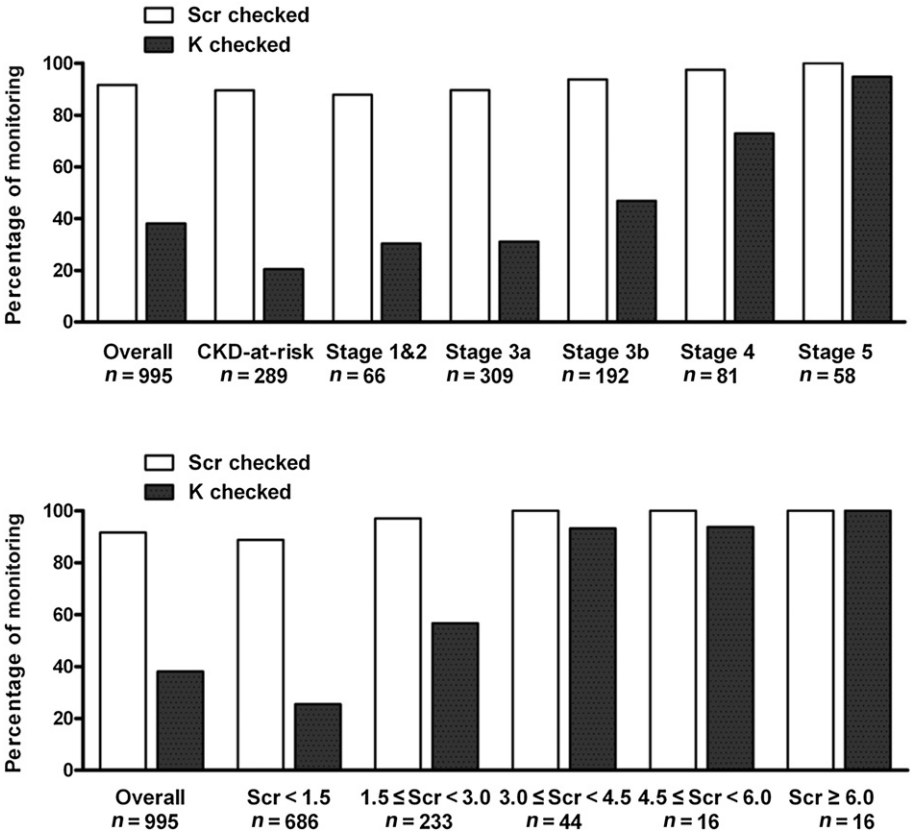

Figure 2. Percentages of serum creatinine (Scr) and potassium (K) measurements in patients who received angiotensin-converting enzyme inhibitor/angiotensin receptor blocker prescriptions, stratified by stage of chronic kidney disease (CKD; upper panel) and by Scr level (lower panel).

Table 3 Factors associated with monitoring of serum creatinine and potassium among the study population (n = 995).

Characteristics	Serum creatinine monitored			Potassium monitored		
	Adjusted odds ratio	95% CI	p	Adjusted odds ratio	95% CI	p
Age (≤50 y as reference)						
51–64	1.11	0.50–2.45	0.80	1.01	0.58–1.56	0.01
≥65	0.55	0.25–1.17	0.12	0.95	0.58–1.56	0.84
Sex (female as reference)	0.94	0.59–1.49	0.80	1.08	0.80–1.46	0.08
eGFR (mL/min/1.73 m^2, ≥60 as reference)						
30–59	1.81	1.09–3.01	0.02	1.57	1.10–2.24	0.01
<30	11.66	2.71–50.19	0.001	7.97	4.59–13.84	<0.001
Potassium measurement (without K^+ data at baseline as reference)	—	—	—	4.98	3.66–6.79	<0.001
Co-morbidities (neither as reference)						
DM alone	3.41	1.06–11.00	0.04	1.09	0.53–2.24	0.81
HTN alone	0.83	0.30–2.30	0.72	0.82	0.41–1.68	0.59
DM and HTN	1.88	0.68–5.21	0.23	1.20	0.61–2.37	0.60

Statistical analysis was carried out using a multiple logistic regression model with adjustment for age, sex, eGFR, potassium level, and co-morbidities, and expressed as odd ratios with 95% confidence intervals. A value $p < 0.05$ was considered statistically significant.
DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; HTN = hypertension.

In clinical practice, physicians more frequently use Scr level as a direct marker of renal function. A similar tendency is also noted for classifications based on Scr level. The percentage of patients prescribed ACEIs/ARBs tended to increase for Scr levels below 4.4 mg/dL, but decreased when the Scr level increased to above 4.5 mg/dL. The trend in prescription percentages among different Scr groupings was similar to that of another study [15], which reported that the percentages of ACEI prescription in patients with chronic renal insufficiency, either with or without diabetes, were similar when the Scr was below 3.9 mg/dL regardless of Scr level, but decreased to less than 20% when Scr was above 4.0 mg/dL. Because the baseline Scr level of 124 mol/L (1.4 mg/dL) or above is one of the factors leading to an acute rise in Scr level [19], physicians may hesitate to prescribe ACEIs as first-line treatment once the GFR reaches 20–25 mL/min or below [22]. Furthermore, almost all the ACEI/ARB trials have excluded those patients with an Scr above 3 mg/dL, except for the study by Hou et al. [23], which recruited patients with an Scr of up to 5 mg/dL. This could also explain why there was a decrease in prescription rate in patients with advanced renal failure in our study.

Multivariable analysis showed that patients with lower renal function were more likely to be prescribed ACEIs/ARBs in our study. This is because the present study also included a higher percentage of patients who visited a nephrologist, and the highest prescription rates were by nephrologists (data not shown). In addition, over 73% of patients who visited nephrologists had an Scr above 2.0 mg/dL. Referral of advanced CKD patients to a nephrologist has been suggested in various studies, citing the rationale of a better quality of care from a nephrology team. Schwenger et al. [22] reported that 64% of patients with a mean Scr of 2.3 mg/dL managed in a nephrology clinic were prescribed with ACEIs/ARBs. The St. Vincent Declaration recommended nephrology referral when the Scr exceeds 200 mol/L (2.26 mg/dL) in order to enable management of renal failure [24]. Therefore, the higher percentage of patients with CKD who visited nephrologists and the higher prescription rates of ACEIs/ARBs in our study indirectly revealed the importance of referring CKD patients to nephrologists as soon as possible. In addition, diabetes and hypertension were two factors that may lead to patients being prescribed ACEIs/ARBs in this study. This is mainly due to the positive clinical outcomes and recommendations found in the guidelines [5–7,9].

Scr was evaluated at least once in approximately 92% of patients after prescription of ACEIs/ARBs during the study period (Fig. 2), but more than 60% of patients who had already been prescribed ACEIs/ARBs for a year did not have their potassium monitored. Multivariable analysis further showed that patients with lower renal function and with previous potassium measurement tended to show an increased likelihood of Scr or potassium monitoring in this study. These results reflect the pattern of physicians' prescribing behavior. Patel et al. [25] reported that monitoring of kidney function was recommended in approximately 63% of patients who had CKD with diabetes or/and hypertension, in compliance with NKF-K/DOQI guidelines. Serum potassium monitoring could have been less frequent because of ignorance of the hazards of hyperkalemia and an overemphasis on Scr measurement in order to obtain

an eGFR to evaluate renal function. However, whether monitoring of Scr and K is applied to avoid the adverse effects of ACEIs/ARBs or for regular follow-up of renal function, it should be encouraged. Therefore, we suggest that, in addition to physicians themselves, other members of the CKD care team, including pharmacists and nurses, could also play a role in improving the frequency of laboratory monitoring and further improve outcomes in CKD.

The potential limitations of our study should be noted. First, the generalizability of our findings may be limited by the fact that this was a retrospective study and was confined to only one hospital. Second, because fewer than 20% of patients with an eGFR over 60 mL/min/1.73 m^2 have a proteinuria measurement, this may underestimate the population in the category with stages 1 and 2 CKD. Third, the entire study cohort had had their Scr monitored during the previous year, and this may indirectly tend to include physicians who routinely preferred Scr monitoring. Therefore, it may overestimate the rate of Scr monitoring.

Conclusions

This study shows that prescription of ACEIs/ARBs is common in patients with CKD with diabetes and/or hypertension, and that the percentages increase with stage of CKD, as suggested by various treatment guidelines. Most patients who received ACEI/ARB medications had their Scr measured, but potassium monitoring occurred less frequently, and this should be improved in clinical practice.

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